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Mild oxidation of benzyl alcohols to benzyl aldehydes or ketones catalyzed by visible light

ABSTRACT

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Introduction

The oxidation of alcohols to aldehydes and ketones was the most important reaction in pharmaceutical and fine chemical industry [1]. Numerous methods have been developed to achieve this goal in the past few decades. Among the oxidation methods of alcohols to aldehydes, stoichiometric oxidants such as MnO₂, hypochlorite, activated dimethylsulfoxide etc. are the most commonly used [2–9], and oxygen has been developed as a green oxidant in recent years [10-16]. However, peroxidation was frequently occurred in these processes. Although metal-free method with tempo derivatives as catalyst have been proposed [17-24], co-catalyst is required and separation of product from tempo is tedious. In recent years, visible light catalysis developed rapidly and a series of achievements have been realized because of its unique single electron transfer (SET) and hydrogen atom transfer (HAT) mechanism [25–34]. For the oxidation of alcohols to aldehydes and ketones by photocatalysis, some progress had also been achieved [35-42]. Das reported the oxidation of alcohol catalyzed by 9-fluorenone in 2018 (Scheme 1a) [35]; Mitsunuma and Kanai disclosed the catalytic acceptorless dehydrogenation of aliphatic alcohols through a ternary hybrid catalytic system in 2020 [42], which solved the challenge of oxidation of aliphatic alcohols under visible light catalysis (Scheme 1b). Although

ature, pressure and peroxidation with only visible light as the green driving force.

Induced by visible light, mild oxidation condition to prepare benzyl aldehydes or ketones have been

developed by using bromotrichloromethane as photochemical oxidant. This method avoids high temper-

predecessors have made some achievements, it is far from enough for such an important and fundamental reaction.

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Bromotrichloromethane is a kind of simple polyhalomethanes, whose bond dissociation energy of C-Br bond is about 55.3 kcal/mol [43]. Therefore, the C-Br bond can be splitted directly by lighting or heating, which produces a free radical initiator or propagator. The free radical produced by bromotrichloromethane can induce hydrogen atom transfer process, which promotes the functionalization of C—H bond [44]. Since Kharasch first reported its application under photocatalysis in 1947 [45], bromotrichloromethane has been widely used in photochemical oxidation/bromination due to its excellent photochemical properties, especially in the reaction involving Ru/Ir complex photocatalysts [46,47]. With the deepening of the research, it was found that bromotrichloromethane as photochemical oxidant has following advantages: (1) it can split to bromine radicals and trichloromethyl radicals under the irradiation of specific wavelength light without any photocatalyst; (2) low price; (3) trichloromethane is the final by-product, which is convenient for the separation and purification of the products. The above advantages made bromotrichloromethane to become the most widely used oxidant in halogenated oxides. We hypothesized that the photocatalytic oxidation of alcohols can be realized by using bromotrichloromethane as mild oxidant.

Result and discussion

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https://doi.org/10.1016/j.tetlet.2021.153234 0040-4039/© 2021 Elsevier Ltd. All rights reserved. In order to realize the viability of the reaction, a model reaction employing benzyl alcohol (**1a**, 0.5 mmol), bromotrichloromethane

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Table 2

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Scheme 1. Visible-light-mediated oxidation of alcohols.

(0.75 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol%) and MeCN (4 mL) was carried out in a Schlenk tube with 7 W blue LED lamp under nitrogen. Delightfully, the desired benzaldehyde 2a was detected in 53% yield after 8 h (Table 1, entry 1). The control experiment showed that no benzaldehvde 2a was detected when the reaction was carried in the dark (entry 18), and only trace of benzaldehyde 2a (entry 17) formed without any photocatalyst. The above control experiments proved that photocatalyst and visible light were indispensable for this reaction. Inspired by this result, several photocatalysts and solvents was further investigated. Among other photocatalyst, $Ir(ppy)_3$ and $Ru(bpy)_3PF_6$ showed activity in this reaction (entry 4, 5). There were no benzaldehyde 2a produced when $Ru(bpz)_3PF_6$ and eosin Y used. Then solvent such as DCE, THF, NMP and DMF were tried and results were negative, compared with that of MeCN. It is worth noting that a large amount of benzyl bromide (entry 6) was generated when reaction carried in DCE. A brief screen of other oxidants revealed that carbon tetrachloride, potassium persulfate and oxygen were not suitable for reaction. When carbon tetrabromide was used, the amount of benzyl bromide increased with prolongation of reaction time. The reaction continued to be carried in acetonitrile and benzyl alcohol disappeared after 24 h with benzaldehyde 2a in 86% yield detected by GC.

Under the optimized conditions, the generality and scope of primary alcohols were subjected to this reaction (Table 2). When halogens such as *p*-fluoro, chloro, bromo and even iodide are

Table 1

Optimization of the reaction conditions^a



Entry	Catalyst	Solvent	Oxidant	Yield%
1	Ir(ppy) ₂ (dtbbpy)PF ₆	MeCN	CBrCl ₃	53
2	EosinY	MeCN	CBrCl ₃	0
3	Ru(bpz) ₃ PF ₆	MeCN	CBrCl ₃	0
4	$Ru(bpy)_3PF_6$	MeCN	CBrCl ₃	34
5	Ir(ppy) ₃	MeCN	CBrCl ₃	41
6	Ir(ppy) ₂ (dtbbpy)PF ₆	DCE	CBrCl ₃	29
7	Ir(ppy) ₂ (dtbbpy)PF ₆	THF	CBrCl ₃	24
8	Ir(ppy) ₂ (dtbbpy)PF ₆	NMP	CBrCl ₃	7
9	Ir(ppy) ₂ (dtbbpy)PF ₆	DMF	CBrCl ₃	31
10	Ir(ppy) ₂ (dtbbpy)PF ₆	MeCN	$(NH_4)_2S_2O_8$	0
11	$Ir(ppy)_2(dtbbpy)PF_6$	MeCN	CBr ₄	47
12	$Ir(ppy)_2(dtbbpy)PF_6$	MeCN	CCl ₄	5
13	Ir(ppy) ₂ (dtbbpy)PF ₆	MeCN	02	0
14 ^b	Ir(ppy) ₂ (dtbbpy)PF ₆	MeCN	CBrCl ₃	73
15 ^c	Ir(ppy) ₂ (dtbbpy)PF ₆	MeCN	CBrCl ₃	86
16 ^d	Ir(ppy) ₂ (dtbbpy)PF ₆	MeCN	CBrCl ₃	81
17	-	MeCN	CBrCl ₃	trace
18 ^e	Ir(ppy) ₂ (dtbbpy)PF ₆	MeCN	CBrCl ₃	0

Scope of the present photocatalytic oxidation for alcohol^a



^a Condition: 1 (0.5 mmol), CBrCl₃ (0.75 mmol), Ir(ppy)₂(dtbbpy)PF₆ (1 mol%), MeCN (4 mL), 7 W blue LEDs, N₂ atmosphere, 24 h, isolated yield.

attached to R¹ benzene ring, the corresponding aldehydes could be obtained in medium to excellent yields (**2b-2e**). Other substrates containing electron withdrawing groups or electron donating groups also showed good tolerance (**2f-2n**). However, a large amount of *p*-methoxybenzyl bromide and *p*-methoxybenzyl chloride were generated in this system with 44% yield of the target product (**2k**). When R¹ is 1-naphthyl and 2-thiophene group, the yield is only 59% and 29% (**2o-2p**). Then aliphatic alcohol was also tried and no product (**2q**) was detected by GC–MS, which may be due to

^a General condition: **1a** (0.5 mmol), oxidant (0.75 mmol), photocatalyst (1 mol%), solvent (4 mL), 7 W blue LEDs, N₂ atmosphere,8h reaction time, the yield was determined by GC. ^b1 equiv. bromotrichloromethane, 24 h reaction time. ^c1.5 equiv. bromotrichloromethane, 24 h reaction time. ^eIn the dark.

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Scheme 2. Oxidant reaction of 1-phenylethane-1-ol.



Scheme 3. Oxidation of benzhydrol via photocatalysis.

the high bond dissociation energy of aliphatic α –C–H or the poor stability of aliphatic α -carbon radicals [41].

Then the scope of secondary alcohols was examined. It was found that, for example, 1-phenylethane-1-ol (**1r**) 1-(4-fluo-rophenyl)ethane-1-ol (**1s**), 1-(4-chlorophenyl)ethane-1-ol (**1t**) and 1-(4-(methylthio)phenyl)ethane-1-ol (**1u**) could be oxidized to ketones, but the α position of ketones suffered from over halogenated in this system. The oxidation results of 1-phenylethane-1-ol (Scheme 2) characterized by ¹H NMR showed that the ratio of acetophenone: α -chloroacetophenone: α -bromoacetophenone was about 1:0.5:0.8 (see Supplementary Information). Diphenylmethanol and 2,2-dimethyl-1-phenylpropan-1-ol can be oxidized to ketones successfully and the by-products of over halogenation were not detected (**1v** and **1u**, Scheme 3).

In order to further explore the mechanism of oxidation process, three equivalents of tempo and 1,1-diphenylethylene were added to the system respectively, and the reaction was inhibited completely (Scheme 4). It can be concluded from above experimental results that the reaction may involve a radical pathway.

According to literature records and experimental results [38,48–50], the reaction mechanism as shown in Scheme 5 is proposed. The BDE of H-CCl₃ (BDE \approx 95 kcal/mol) is much larger than that of benzylic C—H (BDE \approx 79 ± 2 kcal/mol) [43], so a H-abstraction from the benzylic C—H by trichloromethyl radical could be probably achieved. Under irradiation of blue light, the reduction of bromotrichloromethane by *Ir³⁺ gives bromine anion and trichloromethyl radical. Then benzyl alcohol radical intermediate II was obtained by hydrogen atom transfer process between trichloromethyl radical and benzylic C—H of benzyl alcohol I, which were then oxidized to corresponding cationic intermediate III by Ir⁴⁺. Finally, the target product V was produced after deprotonation of intermediate IV.

Conclusions

In conclusion, a mild method for the oxidation of benzyl alcohols to aldehydes and ketones catalysis by visible light was developed. Unfortunately, secondary benzyl alcohols suffered from over



Scheme 4. Exploration of reaction mechanism.



Scheme 5. The plausible reaction mechanism.

bromination and chlorination at α position of ketones and aliphatic alcohols show low activity in this system.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153234.

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